Remarks/Arguments

Claims 9-11 and 14-30 are pending in the application. Claims 14-16, 19-21, 25-27 and 30 are canceled herein. Accordingly, claims 9-11, 17, 18, 22-24, 28 and 29 are presented for examination on the merits.

Claim 9 has been amended to more particularly define the claimed invention. Specifically, claim 9 has been amended to recite that the claimed recombinant enzyme is encoded by a polynucleotide that hybridizes under high stringenecy conditions to the complement of SEQ ID NO: 1, 3 or 5. Support for this amendment is found at page 4, first paragraph, and page 15, second paragraph. Various typographical errors have been corrected in the claims. The language "capable of hydrolyzing" has been amended to "hydrolizes." This amendment does not substantively alter the scope of the claimed subject matter.

I. Rejection of Claims 9 and 18 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendments to claims 9 and 18 render this ground of rejection moot.

II. Rejection of Claims 14, 15 an 20 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendment to claim 9 and cancellation of claims 14 and 20 render this ground of rejection moot.

III. Rejection of Claim 19 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that cancellation of claim 19 renders this ground of rejection moot.

IV. Rejection of Claim 29 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendments to claim 29 render this ground of rejection moot.

V. Rejection of Claims 9-11, 14-17, 19-22, 24-28, and 30 Under 35 U.S.C. § 112, First Paragraph

Claims 9-11, 14-17, 19-22, 24-28, and 30 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification is enabling for only a few specifically disclosed recombinant enzymes, but does not provide an enabling disclosure commensurate in scope with the claims.

Applicants respectfully disagree.

1. The Amount of Disclosure Required For Enablement Is Inversely Proportional To The Predictability of the Claimed Subject Matter.

The amount of guidance or direction that the specification must provide is inversely related to the amount of knowledge in the state of the art, as well as the predictability of the art. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). In other words, if persons skilled in the art already know a lot about the subject matter of the invention, less information must be included in the specification.

To be enabling, a patent specification must teach one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Enzo Biochem, Inc. v. Calgene, Inc.* 188 F.3d 1362, 1371 (Fed. Cir. 1999)(quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)). A determination as to whether the disclosure in a specification properly enables the claims at issue is made "as of the date the patent application was first filed." *Id.* (citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)).

It is respectfully submitted that the specification provides sufficient guidance, and that, coupled with the state of the art concerning the subject matter of the claimed invention at the time of filing the present application, and level of skill in the art of molecular biology is sufficient to meet the enablement requirement of 35 U.S.C. § 112.

The present specification is directed to a recombinant enzyme, malathion carboxylesterase (MCE), and its use for degradation of organophosphate pesticides residues. Applicants have discovered that a variant of the *L. cuprina* LcαE7 gene encodes a MCE enzyme which has organophosphate degradation activity. Using "the wealth of molecular genetic techniques available for *D. melanogaster* to clone the *L. cuprina* MCE homologue" applicants isolated and analyzed the variant gene. [specification p. 2, l. 23-26]. Applicants sequenced the cloned gene and determined the site of the variation responsible for resistance to malathion. Using consensus generic alpha-esterase primers specific for the conserved regions of the multiple amino acid alignments of *D. melanogaster* and *L. cuprina* alpha-esterase genes, Applicants cloned a 534 bp replicon from *M. domestica*, which was then used to screen a genomic library to isolate the full length *M. domestica* gene. [Specification pp. 13-15]. Characterization of the gene product demonstrated that it has the same activity and amino acid alteration at position 251 as the *L. cuprina* MCE. The specification provides a detailed description of the steps used to clone the *L. cuprina* homolog from *M.domestica*. Moreover, all of the molecular biology tools used in the cloning exemplified in the specification are routinely used, and were well known techniques at the time of the invention. Indeed, the PCR primers used to isolate theh second gene were based on known, conserved sequences for this family of esterase genes.

The specification provides at Figure 4 the conserved amino acids of the claimed family of enzymes. The specification also teaches that up to 25% amino acid changes may be made in the

non-conserved regions while maintaining enzyme activity. Thus, the specification provides sufficient guidance concerning which regions of the enzyme sequence can be altered without loss of enzyme activity. Further, the state of the art at the priority date with regard to the structure/function of esterases was well advanced, as evidenced by the literature and declaration of Dr. Robyn Russell provided with the response filed February 17, 2005. Considering the information provided in the specification, and the advanced knowledge of esterase structure/function, it is submitted that more than sufficient guidance has been provided for one of ordinary skilled in the art to produce the molecules of the claimed invention.

Moreover, using the techniques described in the specification, the inventors have a produced a molecule which is **63% identical** to that of the disclosed *L. cuprina* protein which maintains the activity of the claimed protein. More specifically, as discussed in Dr. Russell's Declaration, a W251L mutant of the orthologous protein from *D. melanogaster* was made and shown to possess the claimed activity. The mutant of the protein from *D. melanogaster* shares about 126 amino acids with the corresponding *L. cuprina* protein which **are not** found in the *M. domestica* protein. Furthermore, as outlined in the previously filed Rule 132 Declaration (see paragraph 6), the inventors repeated their efforts and made a further MCE enzyme that has the claimed activity (see paragraph 6 of the declaration). Thus, using the guidance of the specification, and tools and procedures known in the art the skilled person could have readily produced at the priority date which possess the activity of the claimed enzymes.

As demonstrated in the specification and further by the declaration of Dr. Russell, the present specification provides sufficient guidance to the skilled practitioner to enable the isolation or generation of homologs of *L. cuprina* MCE which have the claimed activity. The specification provides an example of cloning of a *M. domestica* gene based on the *L. cuprina*

sequence, and provides amino acid sequence alignment showing which regions of the enzyme may or may not be altered. The claims specifically reflect this disclosure.

That the claims are enabled is strongly supported by (1) the specificity of guidance provided on how to isolate the claimed MCE enzymes; and (2) the disclosure in the specification of amino acid sequence alignments which were successfully used to isolate homologs of *the L. cuprina* MCE, and (3) the scientific literature, which further demonstrates the predictable nature of the MCE sequences.

*One Of Ordinary Skill In The Art Would Not Have To Engage In Undue Experimentation To Isolate and Use the Claimed Enzymes to E*liminate *or Reduce Organophosphate Pesticide Residues*

In determining whether a disclosure requires "undue experimentation," the patent office and the courts frequently consider the following illustrative factors:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

a. *Quantity of Experimentation Necessary*

A patent disclosure is not rendered non-enabling simply because it requires further experimentation. *In re Wands*, 858 F.2d at 737. Routine or conventional experimentation is frequently necessary for one of ordinary skill in the art to practice the invention. That is the case here. As shown in the specification and the Declaration, using well-known molecular biology procedures, a researcher would not have to conduct substantial non-routine experiments to identify MCE enzymes that have the claimed activity.

The scientific literature establishes that one can extrapolate from the amino acid sequence alignment shown in the specification to other amino acid sequences that will preserve the enzymatic activity of the MCE. One of skill in the art would not need more guidance than that provided by the present specification to isolate other MCE enzymes.

b. *Predictability or Unpredictability of the Art and Amount of Direction or Guidance Presented*

The present specification provides two examples of MCE enzymes having the claimed activity and teaches how to isolate others. Indeed, the specification teaches the isolation of a *M. domestica* enzyme based on the sequence of the *L. cuprina* sequence and provides sequence alignment data to enable others of skill in the art to do the same. Applicants did not encounter any difficulties in isolating further MCEs, and did not use anything but routine molecular biology tools to isolate or make the several examples of MCEs encompassed by the claims. Thus, the guidance in the specification is sufficient to enable one of skill in the art to do the same.

Further, and contrary to the Examiner's assertions,given the amount of guidance provided in the specification, this is not an unpredictable art. The sequence alignments shown in Figure 4 show which amino acids cannot be altered and which regions of the sequence may be altered to retain enzyme activity. One of skill in the art would be able to predict, on the basis of the guidance provided in the specification, which amino acid alterations are likely to provide a functioning MCE. Indeed, Applicants have demonstrated this in Dr. Russell's declaration.

Moreover, the claims require that the recombinant enzyme contains the amino acid residues that are conserved with the exception of amino acid 251, and further require that the nucleic acid encoding the claimed recombinant enzyme hybridizes under high stringency conditions with the complement of SEQ ID NO: 1, 3 or 5. These claim limitations place

significant structural limitations on the claimed recombinant enzymes, further increasing the likelihood that the claimed enzyme retains the claimed function.

Presence or Absence of Working Examples

The specification provides a working example demonstrating how the L. cuprina gene may be used to isolate homologs of the enzyme. The specification also provides a disclosure of each of the steps used to characterize any homologs. As discussed above, all of the procedures and tools are routine in the field of molecular biology. Thus, the disclosure of a working example is sufficient guidance to the skilled practitioner to enable the present claims.

The Nature of the Invention, State of the Prior Art and Relative Skill of Those in the Art

The nature of the invention determines the state of the art and the level of skill in the art. The state of the art is what one of skill in the art would have known at the time of filing. It defines the pertinent art, what was well known in the art, the degree of predictability in the art and the amount of guidance that the specification needs to be enabling. The scientific literature relating to the structure and function of the esterases which are the subject of the present claims was well advanced at the time of filing the application, demonstrating that that skilled practitioners had a good understanding how to manipulate these enzymes. Moreover, as discussed in Dr. Russell's declaration, the level of skill in this art is very high, and the procedures used are routine. Thus, the skilled practitioner would have been able to practice the claimed invention at the time of filing on the basis of the guidance provided in the specification.

The Breadth of the Claims

The breadth of the claims refers to the scope of coverage that the claims are afforded. The claim scope should match what is disclosed in the specification and what could reasonably

be obtained based on the invention's contribution to the art. *Plant Genetic Sys., N.V. v. Dekalb Corp. Genetics,* 315 F.3d 1335, 1339 (Fed. Cir. 2003). The scope of enablement provided by the disclosure must be commensurate with the scope of protection being sought. In this case, the present specification provides the sequence of the *L.cuprina* gene and MCE, as well as the tools and procedures used to isolate the enzyme, which were routine at the time of filing. The specification also provides a working example showing how the *L. cuprina* sequence was used to isolate MCE from *M. domestica,* again using processes and tools taught in the specification which were routine in the art. The specification also provides amino acid sequence alignment to which clearly shows which amino acids are conserved across species, and which amino acids are different, *i.e.*, are modified across species.

In conclusion, the specificity of guidance in the specification, coupled with the very high level of skill in the art and the evidence in the scientific literature that much was known about the subject matter of the claimed invention at the time of filing, clearly demonstrate that the present claims are enabled. Accordingly, the rejection of claims 9-11, 14-17, 19-22, 24-28, and 30 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

VI. Rejection of Claims 9-11, 14-17, 19-22, 24-28, and 30 Under 35 U.S.C. § 112, First Paragraph

Claims 9-11, 14-17, 19-22, 24-28, and 30 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification does not provide written description support for the polynucleotides sequences encoding polypeptides within the scope of the genus claimed.

Applicant respectfully disagrees.

The present claims are directed to polypeptides whose structure is defined by the polynucleotide sequences encoding them, and further defined by specific amino acid sequences,

i.e., a specified sequence at position 251 and conserved amino acid sequence is retained. The specification discloses three species of the polynucleotides encoding the claimed polypeptides, and indeed, Applicant has been granted the following patent claim in the parent application, which has the same specification as the present application:

1. An isolated DNA molecule encoding an enzyme capable of hydrolyzing at least one organophosphate selected from the group consisting of carboxylester organophosphates and dimethyl-oxon organophosphates, the DNA molecule comprising a nucleotide sequence having at least 60% homology with Lc.alpha.E7 (SEQ ID NO:7), in which the protein encoded by the DNA molecule differs from E3 (SEQ ID NO:8) at least in the substitution of Trp at position 251 with an amino acid selected from the group consisting of Leu, Ser, Ala, Ile, Val, Thr, Cys, Met and Gly.

Thus, the Examiner's comments and conclusion are not understood, and are clearly not correct. The USPTO has already determined that the specification provides written description support for the genus of polynucleotides encoding the claimed polypeptides.

Further, the claimed polypeptides are defined by the polynucleotides encoding them, *i.e.*, the recombinant enzyme is encoded by a polynucleotide sequence that hybridizes under high stringency conditions to the complement of SEQ ID NO. 1, 3 or 5. Thus, the specification provides sufficient written description of the claimed invention.

All of the claimed recombinant enzymes possess a specified catalytic and includes specified amino acid sequences- the conserved sequences shown in Figure 4. The PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics. . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Guidelines, 66 Fed. Reg. at 1106.

The present specification meets these requirement. Partial amino acid structure is provided, nucleotide sequence structure is defined by hybridization. The function of the claimed polypeptides is also defined. Thus, the specification provides sufficient written description support of the claimed invention.

Accordingly, the rejection of claims 9-11, 14-17, 19-22, 24-28, and 30 under 35 U.S.C. § 112, first paragraph (written description) is respectfully traversed.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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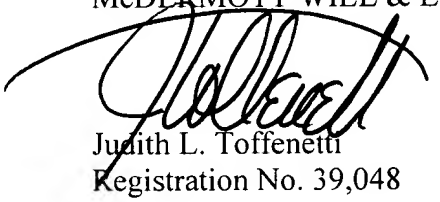

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